

REMARKS

Claims 1, 3-11, 15, 16, 18-26 and 69 remain before the Examiner for reconsideration. Claims 12-14, 17, 27-68, and 70-103 have been withdrawn. Claim 2 has previously been canceled without prejudice.

In the Office Action dated June 22, 2009 the Examiner acknowledged the Request for Continued Examination filed by Applicants on May 18, 2009 and indicated that the finality of the previous Office Action has been withdrawn.

The Examiner rejected Claims 1 and 69 under 35 U.S.C. 112, second paragraph, “as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” Specifically, the Examiner asserted that:

Specifically a polyurethane is claimed, however a reaction between an isocyanate and an amine group (bioactive agent with group —X which can be an amine) would not form a polyurethane but a polyurea. As evidence applicants only have to consider their own remarks filed 05/18/2009, which on the top of page 15 shows a reaction scheme between an isocyanate, water and an amine, the product is a polyurea (-RNHCONHR-) not a polyurethane (-RNHCOOR-).

Applicants have amended claims 1 and 69 to remove the reference to a polyurethane composition and insert a reference to porous foamed polymer composition, thereby obviating the Examiner's rejection. Urea linkages occur within the polymer as a result of a the reaction of water with isocyanate groups, even absent a bioactive agent including an amine group. Applicants respectfully assert that the claims, as amended, fully comply with the requirements of Section 112.

The Examiner rejected Claims 1,3-11,15-16,18-20,22,25,69,104-11 and 112 under 35 U.S.C. 102(e) “as being anticipated by Beckman et al. (US 7,264,823 B2), for the reasons set forth in the office action filed 11/30/2007.”

The Examiner rejected Claims 1,3-4,7-8,12,19,22,27-30,33,69,104-105,108 and 109 under 35 U.S.C. 102(e) “as being anticipated by Woodhouse et al. (US 6,221,997 B1), for the reasons set forth in the office action filed 11/30/2007.”

The Examiner rejected Claims 1,3-11,15-16,18-26,69 and 104-112 under 35 U.S.C. 103(a) "as being unpatentable over Zhang et al. (Biomaterials 21 (2000) 1247-1258) in view of Liptova et al. (Macromol. Symp. 152, 139-150 (2000)) or in view of Woodhouse et al. (US 6,221,997 B1), for the reasons set forth in the office action filed 11/30/2007."

With regard to Applicant's arguments, the Examiner specifically asserted that:

Applicant's arguments filed 11/03/2008 have been fully considered but they are not persuasive.

Applicants assert that none of the references above describe the reaction between a multifunctional isocyanate with a bioactive agent in water. Applicants assert that water exerts an effect on the reaction in that it acts as a chain extender; therefore the examiner cannot ignore the limitation as this leads to a patentable distinction to the polymers chemical structure. As evidence applicants point to their reaction scheme on page 15 that purports to show the reaction product between an isocyanate, water and an amine and their belief that water is a fundamental aspect in the formation of the polyurethane.

The examiner respectfully disagrees. Firstly it is noted by the examiner as pointed out in the 112 2nd paragraph rejection above that the product applicants describe at the top of page 15 is a polyurea not polyurethane. Applicant's arguments seem to revolve around their belief that the chain extender water leads to a patentable difference to the references above. The examiner notes that applicant's claims are drawn to a polyurethane composition formed from the reaction of an isocyanate, water as a chain extender and a bioactive agent. Applicants believe that the reaction with water during the process to make the polyurethane leads to a patentable difference, however as currently amended there is simply no physical characteristic claimed for the polyurethane compositions that would preclude any of the rejections above. Whatever role water plays in the reaction sequence it does not change the chemical structure, the fundamental repeat unit $(-RNHCOOR-)_n$ of polyurethane. While the limitation detailing the use of aliphatic isocyanates and a bioactive agent containing at least one reactive group must be considered by the examiner since their use changes the structure of the polyurethane, the chain extender, water does not change the chemical structure of the polymer. Chain extenders are generally used in the art to functionalize the end groups of a macromolecule or prepolymer, allowing it to further react with another polymeric block, increasing the overall molecular weight of the polymer. Chain extenders are generally used to increase the molecular weight of a polymer; however applicants do not claim a molecular weight within their own claims that would preclude any of the references above. Thus the only physical characteristic of the polymer that would be affected by the chain extender water is not present within the claims. Furthermore applicants note at paragraph [0008] within their own specification that Zhang and coworkers used water as chain extenders for the

prepolymers, Zhang also states that water is used as a chain extender within the abstract. Also Beckman describes using water in reactions of LDI and glucose to make a foamed material. See col 8 lin 21-55.

Applicants further assert there is no disclosure or suggestion within Zhang that details the reaction of a protein or any other bioactive agent with a multifunctional isocyanate compound and Zhang does not even mention what is meant by incorporation of proteins.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Clearly the examiner noted that Zhang while disclosing the peptide based urethane polymer may allow incorporation of proteins of interest such as cell attachment and/or growth factors but does not give any working examples, which is why the reference was combined with the other two other references in a 103(a) obviousness type of rejection. From the disclosures of Liptova and Woodhouse it would have been obvious to one of ordinary skill in the art that polyurethanes of Zhang could be conjugated to bioactive substances such as peptides and heparin.

Applicants respectfully traverse the Examiner's rejections and address each rejection below.

Claims 1,3-11,15-16,18-20,22,25 and 69 are not anticipated under 35 U.S.C. 102(e) by Beckman et al. (US 7,264,823 B2)

To assert anticipation under Section 102(b) the Examiner must show that each element of the claim in issue is found, either expressly described or under principles on inherency, in the cited reference. Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 771, 218 USPQ 781, 789 (Fed. Cir. 1983), cert. Denied, 465 U.S. 1026 (1984); Tyler Refrigeration v. Kysor Industrial Corp., 777 F.2d 687, 689, 227 USPQ 845, 846-47 (Fed. Cir. 1984) (judgment of anticipation reversed). "The test for determining if a reference anticipates a claim of a patent is whether the reference contains within its four corners adequate directions for the practice of the patent claim" Kistler Instrument A.G. v. United States, 628 F.2d 1303, 1311, 203 USPQ 511, 519, aff'd, 211 USPQ 920 (Ct. Cl. 1980). The reference, whether foreign or domestic, patent or otherwise, must be construed strictly for what it "clearly and definitely discloses." Application of Boling, 292 F.2d 306, 310-11, 130 USPQ 161, 164 (CCPA 1961); Aluminum Co. of Am. v. Sperry Products, Inc., 285 F.2d 911, 922, 127 USPQ 394, 403 (6th Cir. 1960), cert. denied, 368 U.S. 890 (1961). A patent is not

anticipated by a reference “unless the latter exhibits the invention in such full, clear and exact terms as to enable any person skilled in the art to practice it without making experiments.” 285 F.2d at 922, 127 USPQ at 403.

Applicants respectfully assert that, under the appropriate standard as set forth above, Beckman et al. does not anticipate the presently claimed compositions and implants. Unlike the porous, foamed polymer compositions of the present invention, adhesives and other isocyanate-functional compositions of Beckman et al. are formed in the absence of water. In that regard, in the case of Beckman et al., all multi-functional precursor compounds or reactants thereof which include reactive hydrogen groups (-OH groups and/or -NH₂ groups), are first reacted with an excess of a multi-functional isocyanate such that all reactive hydrogen groups are reacted to provide an isocyanate-capped prepolymer. See, for example, Col. 9, lines 33-38. As set forth previously, the presence of water in the reactions of Beckman et al. would cause reaction of all isocyanate functionality in the compounds of Beckman et al., and thereby render the compounds of Beckman et al. ineffective as adhesives.

Unlike the adhesives of Beckman et al., in the presently claimed compositions and implants, multifunctional isocyanate compounds are reacted with at least one bioactive agent in a solution with a chain extender comprising water. The bioactive agents are not first capped with isocyanate functionality in the absence of water as set forth in Beckman et al. To the contrary, in the presently claimed compositions, the multifunctional isocyanate compounds simultaneously react with the bioactive agent and with the water (destroying any free isocyanate groups) in forming porous foamed compositions inherently including urea linkages (as a result of the reaction of the multifunctional isocyanate compounds with water) distributed throughout the porous foamed composition.

As recognized by the Examiner, Beckman et al. also discloses the formation of highly crosslinked prepolymers formed from glucose (a monosaccharide and a carbohydrate) and lysine diisocyanate in the absence of water in which glucose molecules (polyols) are interconnected by polyurethane linkages. Prior to complete reaction, samples of such prepolymers were withdrawn and reacted with water to form foams. Col. 8, lines 39-55. The composition of such a polymer is quite different from a polymer in which glucose is reacted with a multi-functional isocyanate while

in a solution with a chain extending comprising water. Nonetheless, Applicants have removed carbohydrates from the bioactive agents set forth in the claims.

Beckman et al. does not disclose or suggest, reaction of multi-isocyanate compounds with any of the biologically active agents of the present claims in solution with a chain extender comprising water to form the porous, foamed polymer compositions of the present claims.

Claims 1,3-4,7-8,12,19,22,27-30,33 and 69 under are not anticipated under 35 U.S.C. 102(e) by Woodhouse et al. (US 6,221,997 B1)

Applicants respectfully assert that, under the appropriate standard as set forth above, Woodhouse et al. does not anticipate the presently claimed compositions and implants. Although Woodhouse et al. discloses the incorporation of amines or oligopeptides into the polymers thereof, the amines or oligopeptides are first reacted with another component to be formed into a chain extender including the amine or oligopeptide. See, for example, formulas (A), (B) and (c) of in cols. 2 and 3. In that regard, Woodhouse et al. discloses esterification reactions between amines and diols such as 1,4 cyclohexane dimethanol to form the chain extenders thereof. See, for example, Fig. 1, col. 8, lines 53-61 and the claims. Woodhouse et al. does not disclose reaction of an amine or an oligopeptide directly with a multi-functional isocyanate as in the presently claimed compositions and implants. Further, the reactions of Woodhouse et al. occur in the absence of water. Once again, in the presently claimed compositions and implants, multifunctional isocyanate compounds simultaneously react with the bioactive agent and with the water in forming a porous foamed composition inherently including urea linkages (as a result of the reaction of the multifunctional isocyanate compounds with water) distributed throughout the porous foamed composition. The presently claimed foamed polymer compositions are very different from the polymers of Woodhouse et al. in their chemical composition and in their physiochemical properties.

Section 103

Claims 1,3-11,15-16,18-26 and 69 under are not unpatentable under 35 U.S.C. 103(a) over Zhang et al. (Biomaterials 21 (2000) 1247-1258) in view of Liptova et al. (Macromol. Symp. 152, 139-150 (2000)) or in view of Woodhouse et al. (US 6,221,997 B1)

Zhang et al. discloses the reaction of glycerol with lysine diisocyanate in the absence of water to form a crosslinked prepolymer in which glycerol residues are interconnected or crosslinked via urethane linkages. Water was then added to the prepolymer to induce further crosslinking and foaming. Even with respect to glycerol, Zhang et al. does not disclose reaction of the glycerol in a solution with a chain extender comprising water such that the glycerol and the water is reacted with the diisocyanate simultaneously in forming a foamed polymer composition.

As recognized by the Examiner, on page 1248, Zhang et al. further indicates that the LDI-glycerol polymers thereof may allow incorporation of proteins of interest. As admitted by the Examiner, Zhang et al. is not enabling for covalent attachment of proteins within the polyurethane thereof. Zhang does not disclose even what is meant by “incorporation of proteins.” Once again, native, unreacted proteins may be entrapped within the polymer matrix or within the pores of the polymer foam without any reaction of the proteins.

In any event, there is absolutely no disclosure or suggestion in Zhang et al. of reaction of a protein (or any other bioactive agent or other compound) in a solution with a chain extender comprising water with a multi-functional isocyanate.

Furthermore, for the reasons set forth above and in previously filed responses, one cannot combine the disclosure of Zhang et al. with the disclosure of Lipatova et al., Woodhouse et al. and/or any combination thereof to arrive at the present invention. Lipatova et al. and Woodhouse et al. disclose the incorporation of various entities into a polyurethane polymer. However, neither Lipatova et al. nor Woodhouse et al. disclose or suggest reaction of the least one multifunctional isocyanate compound with at least one bioactive agent in a solution with a chain extender comprising water as set forth in the present claims so that the multifunctional isocyanate compound reacts with the at least one bioactive agent and with the water to form a porous foam. Indeed, the polymers of Lipatova et al. and Woodhouse et al. are formed in the absence of water.

As set forth herein, and contrary to the Examiner's assertion, the presence of water, which is highly reactive with isocyanate functionalities to form urea linkages, affects the chemical composition and physiochemical properties of a polymer. The polymer compositions of Zhang et al., Lipatova et al. and Woodhouse et al. are quite different from the presently claimed polymer composition.

Although the Examiner is correct that one cannot show nonobviousness by simply attacking references individually where the rejections are based on combinations of references, this means only that a reference cannot be read in isolation and must be read for what it fairly teaches one skilled in the art in combination with the prior art as a whole. *In re Merck & Co.*, 800 F.2d 1091,231 USPQ 375 (Fed. Cir. 1986). It is well established that, in determining obviousness, one must determine the scope and content of the prior art and ascertain the differences between the prior art and the claims at issue. *Graham v. John Deere* 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545, (1966). The Examiner cannot ignore the Graham requirement of establishing that all the elements of the claimed invention are set forth in the prior art by simply asserting that the Applicants cannot attack references individually.

In view of the above amendments and remarks, Applicants respectfully requests that the Examiner, indicate the allowability of the Claims, and arrange for an official Notice of Allowance to be issued in due course.

Respectfully submitted,
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